Systematic Reviews

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Association between impairment of lung function and risk of anxiety and depression in patients with chronic obstructive pulmonary disease—a systematic review

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Abstract

Background This systematic review aims to examine the association between impairment of lung function and risk of anxiety and depression, respectively, in patients with chronic obstructive pulmonary disease (COPD).

Methods Literature search were performed 29/01–2024 using Embase and PubMed. Publications reporting association between forced expiratory volume in one second in percentage of expected value (FEV1(%)) and either anxiety or depression or both in patients with COPD were included. The studies were quality assessed using the Newcastle Ottawa Scale. The studies were analysed by assessing whether they showed significant results or not, and if they showed a negative or positive association between lung function and risk anxiety or depression and a pooled analysis was conducted.

Results Thirty-seven studies were included in the review, 15 reported anxiety and 31 reported depression, with 9 reporting both outcomes. Most were observational studies. Study population sizes ranged from 40 to 2147 patients. Three studies found a significant negative association between anxiety and FEV1(%), while five studies found a positive non-significant association between anxiety and FEV1(%). Fifteen studies found a significant negative association between FEV1(%) and depression. Especially the studies with larger study population sizes showed significant results. The pooled analysis supported this, as the depression studies showed a significant association between depression and FEV1(%), while the anxiety studies showed part non-significant, part significant associations between anxiety and FEV1(%).

Conclusion This systematic review did not support an association between anxiety and impairment of pulmonary function as only 3/15 studies showed significant negative associations, and some studies showed positive associations. This review indicated an association between depression and impairment pulmonary function in patients with COPD, as most studies with a larger study population size showed a significant negative association.

Sytematic review registration.

PROSPERO 2024 CRD42024506065 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024506065

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Keywords Pulmonary function, Depression, Anxiety, Forced expiratory volume, Chronic obstructive pulmonary disease

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common disease, and the third leading cause of death in the world [1]. In patients with COPD comorbidities are of great importance. Among these, studies have shown a prevalence of anxiety in patients with COPD ranging from 13–46%, while the prevalence of depression is found to be 27%, in both cases higher than the general population [2, 3]. Anxiety and depression in patients with COPD have been shown to both increase mortality, decrease health related quality of life and increase the risk of exacerbations [4, 5]. Patients with COPD and comorbid anxiety or depression pose a higher economic burden to the society, compared to patients with COPD without those comorbidities [6]. Therefore, the prevention, diagnosis, and treatment of anxiety disorders and depression in the COPD patient population is important from both an individual and societal point of view. Several risk factors of anxiety and depression in patients with COPD have been suggested, even though there are inconsistencies between studies. Some studies found a lower risk of anxiety with increasing age [7, 8], while other studies found no association [9, 10]. Previous studies found an association between female sex and anxiety [11, 12], while a link between female sex and depression was not significant [7, 9, 11].

It is not clear whether an increase in the disease severity of COPD increases the risk of anxiety, especially because the definition of disease severity differs between studies. While some studies found a higher risk of anxiety with more severe Global Initiative for Chronic Obstructive Lung Disease (GOLD) group and Medical Research Council Dyspnoea Scale (MRC) [7, 13, 14], other studies found no link between MRC scale, 6-min walk test distance [6MWT] and anxiety risk [8, 9]. A 6-min walk test measures the distance a patient can walk in 6 min, thus being a way of measuring functional capacity of the patient [8].

Results are less conflicting in studies investigating the association between depression and COPD, yet also dependent on how disease severity of COPD was evaluated. There are strong associations between higher MRC-score and risk of depression [8, 9, 15, 16], but inconsistent results were found between 6MWT and depression, as some studies found an association [8, 15], but other studies found no association [8, 13, 16].

The impairment of pulmonary function in patients with pulmonary diseases can be measured with spirometry. The Forced Expiratory Volume in one second (FEV1) can be reported using volume in liters or percentage of the expected value for certain sex, age, height, and ethnicity. FEV1 is usually decreased in patients with COPD and is a way of measuring the degree of pulmonary impairment in patients with COPD [17–19].

Although MRC and 6MWTare both validated, subjective scores may be influenced by multiple factors [20, 21]. Therefore, generalisability of the association between an objective measure and anxiety and depression could have higher impact, for example pulmonary function. The results from a 6MWT and FEV1 have been found not to be directly comparable, as several factors affect the performance in the 6MWT [22]. The same applies to associations between MRC-score and FEV1 [23–25]. FEV1 is an objective and well-validated measure of pulmonary function in patients with COPD, although the measurement includes possible sources of error [17–19].

The primary aim of this systematic review is therefore to investigate whether there is an association between lung function impairment defined as FEV1 in relation to expected value and anxiety or depression in patients with COPD.

Methods

Search strategy

This study was conducted as a systematic review with two evaluators on the 29th of January 2024.

A literature search was conducted using PubMed and Embase with the help of an experienced medical librarian. The keywords searched were "Chronic obstructive pulmonary disease" and "Forced Expiratory Volume" and either "depression" and/or "anxiety", both as MeSH and Emtree-terms and as broad search. Common synonyms as such were also included in the search. All English studies published between January 1975 and January 2024 were included. The reference lists of eligible studies were searched to identify other relevant studies. The whole search string is available in Appendix 1. The search was conducted, and the review was prepared according to the PRISMA-guidelines, adhering to the PRISMA-checklist [27].

The protocol was submitted to The International Prospective Register of Systematic Reviews (PROSPERO) prior to implementing the search [28].

Selection criteria.

Only studies exclusively including patients with spirometry verified COPD according to

GOLD-recommendations were included in this review, as only patients with COPD are within the scope of this systematic review [29]. As FEV1 is influenced by sex, age, ethnicity, and height [24], only studies using FEV1 in percentage of expected value (FEV1(%)) or Z-score for calculations were included. Studies were eligible if they reported a numerical risk of anxiety or depression compared to measured FEV1(%) or Z-score, combined with a p-value. Studies were eligible if anxiety or depression were defined as one of the following: A verified depression or anxiety scale, the use of medication or hospital diagnosis. Studies concerning both anxiety and depression were included, but only if they differentiated between anxiety and depression as separate diagnoses in the analysis, as a separate analysis of anxiety and depression will take place.

Exclusion criteria were other pulmonary diseases than COPD, either as only respiratory disease or in conjunction with COPD and studies of mixed populations, that is studies with both patients with COPD and healthy subjects within the study population. Studies only reporting e.g. health related quality of life or unspecified mental illness were excluded.

The titles and abstracts were screened by two independent evaluators using EndNote. Any study evaluated to be eligible by any evaluator underwent full text review by one evaluator. In case of disagreement on inclusion a third evaluator was consulted. The number of excluded studies and the reason for exclusion were noted in PRISMA flow chart (Fig. 1).

Every study was assessed regarding risk of bias with a version of Newcastle Ottawa Quality Assessment Scale (NOS) adapted for cross-sectional studies by one evaluator. As NOS was originally made for case–control or cohort studies, the scale was modified to fit cross-sectional studies [30]. Three main categories were assessed: Selection (representativeness, sample size and non-respondents), comparability (If the study controls for any factors), and outcome (Assessment tool and statistical test used). The main highlights of the bias assessment were discussed in the discussion section. Scale and results can be seen in Appendix 2–3.

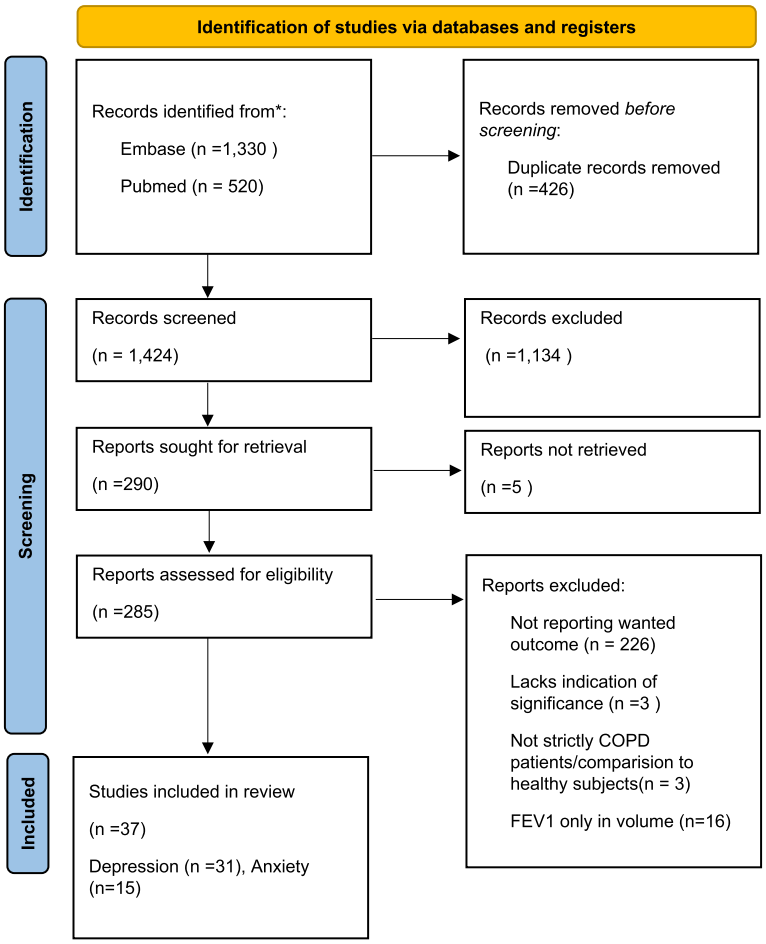

Fig. 1 Flowchart describing selection process of eligible studies (27)

Data extraction and analysis.

Outcomes were either depression or anxiety compared to FEV1(%) or Z-score. The selected articles were divided into two groups, either concerning depression or anxiety, but could also be included in both groups if both outcomes were reported separately. For each study, study population, number of participants, study type, and anxiety and depression definition and prevalence were recorded. Moreover, basic information consisting of first author and year was recorded. The findings of the studies were recorded using the statistical outcome measure presented in the article (e.g. relative risk, odds ratio, hazard ratio, correlation coefficient, mean difference) combined with *p*-value.

The studies were grouped according to size based on number of participants to evaluate the influence of study size on significance. The studies using the two most common outcome measures were used in pooled analysis using MedCalc software version 23.0.1. Random effects in the calculations were assumed, as the effect size of FEV1(%) was assumed to vary across study settings.

Results

Selection process

The selection process is presented in Fig. 1. Twenty-two studies which only reported FEV1(L), had study populations that did not meet the inclusion criteria or did not report anxiety or depression in an appropriate way were excluded and are presented in Appendix 4. Of the 37 studies included, 15 were allocated to the anxiety group and 31 were allocated to the depression group, as 9 studies reported both outcomes. The studies were published between 2002 and 2023. None of the studies used Z-values to define FEV1 in relation to reference measures, so FEV1(%) will be as definition of pulmonary function onwards.

Study results

Anxiety

The studies reporting anxiety are presented in Table 1. Fifteen studies were included. Most studies (13/15) were observational, the remaining intervention studies, and study population sizes varied from 40 to 2147. The prevalence of anxiety in the studies was between 9.9% to 54.5%. Of the included studies twelve studies showed non-significant results.

Definitions of anxiety were The State Trait Anxiety Inventory (STAI) ($N=5$), Hospital Anxiety and Depression Scale Anxiety Inventory (HADS-A) ($N=4$), Anxiety Disorder Interview Schedule IV (ADIS IV) ($N=2$), Hamilton Anxiety Rating Scale (HAM-A) ($N=1$), Beck Anxiety Inventory (BAI) ($N=1$), Generalized Anxiety Disorder 7 item (GAD) ($N=1$) and Anxiety Inventory for Respiratory Disease ($N=1$). In all the rating scales, a higher score means a higher risk of anxiety.

Range of age differed from > 18 years of age to no age restrictions, as 9/15 of the studies did not mention age restrictions. Nine studies recruited patients from outpatient clinics, one both outpatient and inpatient, three from rehabilitation programs and two from cohort studies. Five studies were conducted in Europe, three in Asia, three in Africa (specifically Egypt), two in Australia, one in the Northern America and one in Southern America.

The number of significant studies relative to the size of the study populations in the anxiety group is presented in Fig. 2.

The pooled correlation coefficient calculation included 7 studies and showed a non-significant negative association between FEV1(%) and anxiety, with a correlation coefficient of –0.156 (*p*-value 0.184) (Fig. 3A). The pooled standardized mean difference calculation included 4 studies and showed a significant association between anxiety and FEV1(%), with a standardized mean difference of –0.229 (*p*-value 0.033) (Fig. 3B).

Depression

The studies reporting depression are presented in Table 2. Thirty-one studies were included. Most studies were observational (29/31), the remaining were intervention studies. Study population sizes varied between 54 to 2147. The prevalence of depression in the studies was between 5.8% to 54.7%. One study [53] used two completely different study populations with two different sets of results, and therefore these results will be presented as two studies, meaning we will count the included studies as 32 in the further analysis. A significant association between FEV1(%) and depression was found in 15 studies.

Definitions of depression in included studies were Center for Epidemiologic Studies Depression Scale (CES-D) ($N=4$), Becks Depression Inventory (BDI) ($N=7$), Brief Assessment Schedule Depression Cards (BASDEC) ($N=1$), Geriatric Depression Scale (GDS) ($N=4$), Hospital anxiety and depression scale for depression (HADS-D) ($N=5$), Hamilton Depression Rating Scale (HAM-D) ($N=3$), Self-rating Depression Scale (SDS) ($N=2$), Medical history ($N=1$), Personal Health Questionnaire 9 (PHQ-9) ($N=4$) and Mini international neuropsychiatric interview plus ($N=1$). In all the rating scales, a higher score means a higher risk of depression.

Of the included studies 15/31 did not mention any age restrictions. Patients under the age of 40 were excluded in ten studies. While seventeen of the studies included patients in outpatient clinics, six studies used registries or existing cohort studies. The rest were included at rehabilitation centre (2), general practice (2), inpatient (1)

Table 1 Studies allocated to the anxiety group

Name	Study type	Subjects	Patient population	Anxiety Prevalence	Anxiety definition	Results	Significant association?
Di Marco 2006 [9]	Observational	202	From a Respiratory Unit, Italy	28.2%	STAI > 45	Anxiety prevalence compared in GOLD group 1–4. P-value 0,256	No
Livermore N 2008 [31]	Case–Control	40	From an outpatient clinic, Australia	Unknown	ADIS-IV	FEV1 (%) compared between patients with panic disorder (80.1%) and no panic disorder (82.2%) (P-value 0.71)	No
Howard C 2009 [32]	Observational	59	From a cardiothoracic centre, UK	35%	HADS-A > 11	Correlation coefficient between anxiety and FEV1(%) 0.005 (p-value > 0.05)	No
Funk GC 2009 [33]	Observational	122	From an outpatient clinic, Austria, > 18 years	49%	HADS-A > 8	FEV1 (%) compared in patients with anxiety (40.5%) and no anxiety (48.3%) (p-value 0.025)	Yes
Livermore N 2012 [34]	Observational	62	From a Respiratory Medical Department, Australia, COPD stage GOLD II-III	40.3	ADIS-IV	FEV1 (%) correlation with panic, correlation coefficient β = -0.05 (p-value 0.04)	Yes
Suh S 2013 [35]	Observational study	30	From a pulmonary rehabilitation program, USA	50%	STAI	FEV1(%) compared between patients with anxiety (55.7%) and no anxiety (52.4%) (p-value > 0.05)	No
Tselebis A 2013 [36]	Intervention study	101	From a rehabilitation program, Greece, < 80 years	25–47.6%	STAI	Correlation coefficient between anxiety and FEV1 (%) r = 0.034 (p-value > 0.05)	No
Elassal G 2014 [37]	Case–control	80	Out- and inpatients, Egypt	22.5%	HAM-A	Correlation coefficient between anxiety and FEV1(%) r = -0.182 (p-value 0.108)	No
Yohannes AM 2016 [38]	Observational	257	From a rehabilitation program, United Kingdom	29.2%	AIR > 8	Correlation coefficient between FEV1 (%) and anxiety r = 0.02 (p-value 0.82)	No
Allam AH 2017 [39]	Observational	150	From an outpatient clinic, Egypt, > 18 years	22%	HADS-A > 11	Correlation coefficient between FEV1 (%) and anxiety r = -0.66 (p-value 0.001)	Yes
Hieba E 2021[40]	Observational	110	From an outpatient clinic, Egypt	54.5%	STAI > 38	Correlation coefficient between anxiety and FEV1 (%) r = −0.178 (p-value 0.063) Correlation coefficient between anxiety and GOLD stage (%) r = 0.194 (p-value 0.042)	No/Yes
Yoshida M 2022 [41]	Intervention study	60	From an outpatient clinic, Japan	9.9–10.2%	STAI	Distribution of subjects in GOLD 1–4 with anxiety (GOLD1 11.27% –GOLD 4 12.0%) compared with whole cohort (p-value 0.147)	No

Table 1 (continued)

Name	Study type	Subjects	Patient population	Anxiety Prevalence	Anxiety definition	Results	Significant association?
Hernández-Pérez A 2022 [42]	Observational	291	From an outpatient clinic, Mexico, 60–85 years,	11.3%	HADS-A > 8	Correlation coefficient between FEV1(%) and anxiety r = 0.009 (p-value 0.873)	No
Hong YJ. 2023 [43]	Observational	2147	From a cohort study, Korea, > 40 years,	19.3%	BAI > 8	Distribution of subjects in GOLD 1–4 in patients with anxiety (GOLD1 13.1% –GOLD4 9.6%) and without (GOLD1 15.1% –GOLD4 6.2%) (p-value 0.319)	No
Liu M 2023 [44]	Observational	226	From a cohort study, China, > 40 years old	22.1%	GAD7 > 5	FEV1 (%) compared in patients with anxiety (62.9%) and no anxiety (67.4) (p-value 0.204)	No

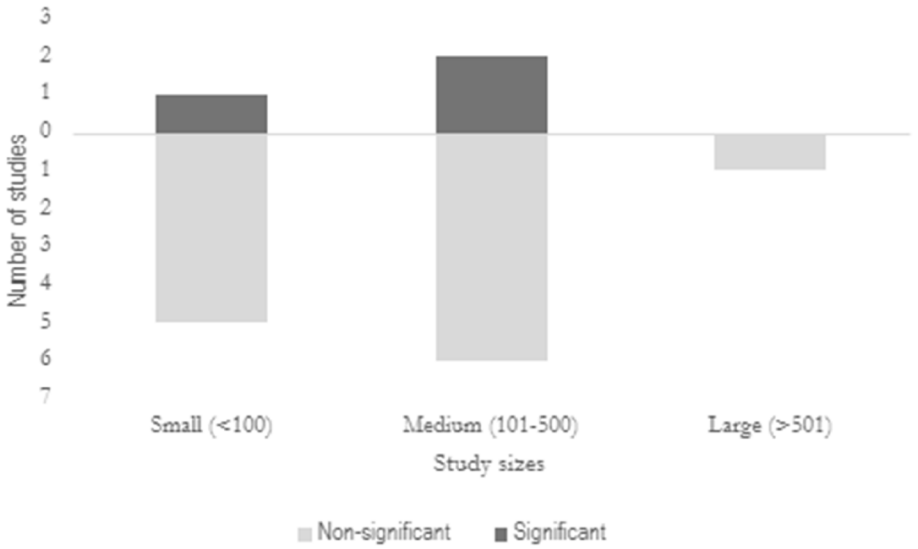

Fig. 2 Number of studies significant and non-significant results compared to sample sizes in the anxiety group. The light downward parts are studies showing non-significant results and the dark upward parts are the studies showing significant results

and inpatient and either outpatient or rehab (2). Thirteen studies were conducted in Europe, eleven in Asia, four in North America, one in South America and two in Africa.

There was a trend against significant outcome being dependant on study size in the depression group (Fig. 4). All but one (6/7, 85.7%) study with a large study population found a significant association between FEV1(%) and depression while four of the studies in the group of small studies (4/9, 44.4%) showed significant association. In the medium group every third study showed significant results (5/16, 31.3%).

The pooled correlation coefficient calculation included 8 studies and showed a significant negative association between FEV1(%) and depression, with a correlation coefficient of –0.173 (*p*-value 0.026) (Fig. 5A). The pooled standardized mean difference calculation included 12 studies and showed a significant association between depression and FEV1(%), with a standardized mean difference of –0.676 (p-value 0.009) (Fig. 5B). One study was excluded from the calculations as it did not report the necessary standard deviation for mean FEV1(%) [16].

Risk of bias assessment

The scores of the risk assessment ranged between 3/8 and 7/8, with a median of 5. Only seven studies obtained any points at all in the 'Comparability' assessment, and fourteen in the 'non-respondents' assessment.

As statistical analysis with p-value and appropriate definition of outcome were parts of selection criteria, all studies scored the maximum of two stars in the 'Outcome' evaluation. All studies also obtained the pulmonary function in an appropriate way, as spirometry verified COPD was a part of selection criteria. Therefore, all studies scored at least 3/8 points.

The studies investigating anxiety obtained a median of 6 points out of 8 (between 4 and 8). The studies investigating depression obtained a median of 6 points out of 8 (between 3 and 8). The studies showing significant results obtained a median of 6 points out of 8 (between 4 and 8), while the non-significant studies obtained a median of 6 points out of 8 (between 3 and 7).

Further details about Risk of bias assessment are available in Appendix 3.

Discussion

This study found no association between anxiety and lung function impairment, defined by FEV1(%) in most studies, but a potential association between depression and FEV1 (%).).

Associations between anxiety and impairment of pulmonary function

Most studies show no association between anxiety and FEV1(%). There are even studies showing positive correlation coefficients or higher FEV1(%) in patients with anxiety compared to patients without anxiety [32, 35, 36, 38, 42].

Three studies by Funk et al. 2009 [33], Livermore et al. 2012 [34] and Allam et al. 2017 [39] found a significant negative association between FEV1(%) and anxiety, while one study by Hieba et al. 2021 [40] found a slightly significant association with GOLD stage 1–4 but not FEV1(%). These studies had small to medium study sizes (62–150), so the significant association cannot be explained by

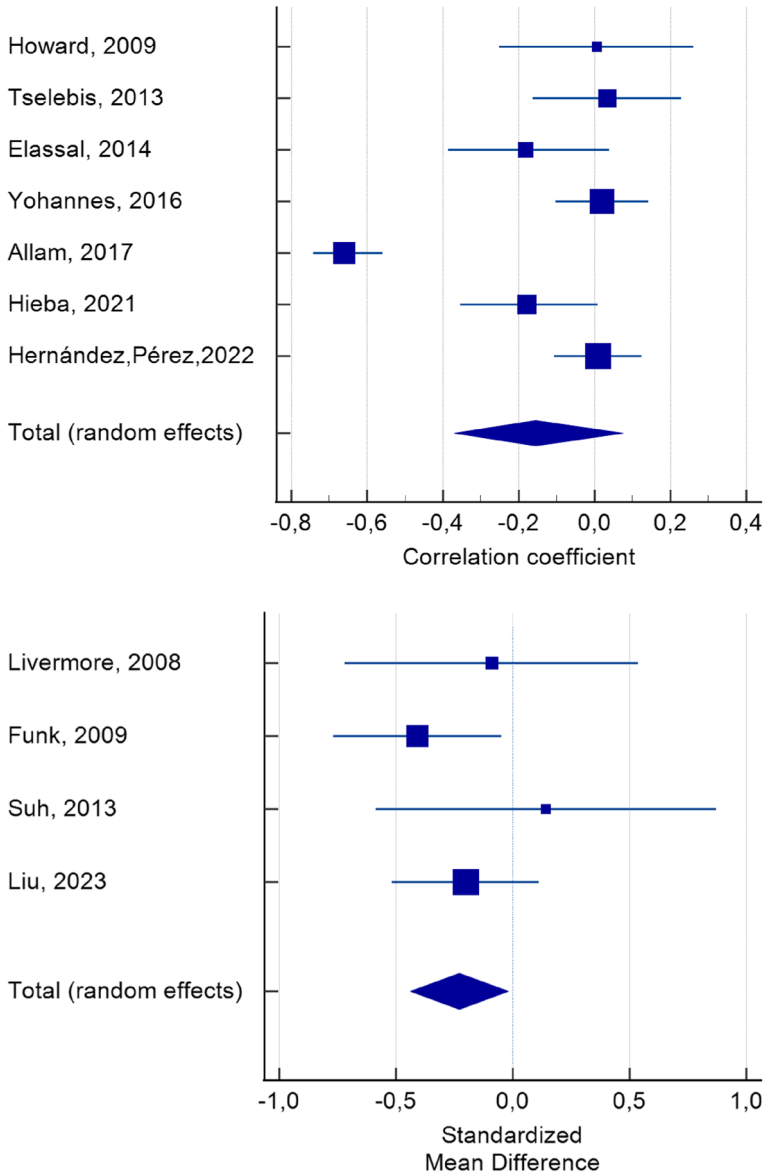

Fig. 3 **A** Pooled correlation coefficients including the studies reporting a correlation coefficient as a measure of association between anxiety and FEV1(%), **B** Pooled standardized mean difference including the studies reporting mean FEV1(%) in patients with anxiety compared to without anxiety

study size. The study population sizes of the anxiety group were generally small, as only one study with a large study population was included.

The prevalence of anxiety was relatively inconspicuous in the significant studies (22–54.5%) compared to the other studies in the anxiety group (Table 1), and comparable to the studies showing positive non-significant associations (11.3%-50%) [32, 35, 36, 38, 42]. The differences in anxiety prevalence could be due to the use of different rating scales in different study populations. However, there does not seem to be a pattern in the use of anxiety rating scales, as e.g. two of the significant studies and two of the studies obtaining positive, but non-significant associations used HADS-A, though cut-off varied between 8–11 [32, 33, 39, 42]. Though, a previous study on patients with Parkinson's disease found a high association among various anxiety scales [65].

The three significant studies were conducted in outpatient clinics in Australia, Egypt, and Australia respectively. The study population in Livermore et al. [34] included only patients in GOLD groups II and III, whereas Allam et al. [39] and Funk et al. [33] included

Table 2 Studies allocated to the depression group

Study	Study type	Subjects	Patient population	Prevalence of depression	Depression definition	Results	Significant?
van Manen JG 2002 [45]	Observational	163	From general practice, Netherlands	21.6%	CES-D > 16	FEV1 < 50% Adjusted OR 0.8 (CI 0.3–2.5) for depression compared to FEV1 > 50%	No
NH Chavannes 2005 [46]	Observational	147	From general practices, Netherlands	27.2%	BDI > 10	OR 1.0 (CI 0.98–1.02) of average FEV1 (%) in patients with depressive symptoms compared to patients without (p-value > 0.05)	No
Di Marco 2006 [9]	Observational	202	From an outpatient clinic, Italy	18.8%	SDS > 50	Prevalence of depression in GOLD group 1–4, comparison between groups. P-value 0,636	No
Al-shair K 2009 [47]	Observational	122	Recruited from media advertising, a Medicines Evaluation Unit, and Outpatient clinic, England	1: 18.9% 2: 23.7%	1: BASDEC > 7 or 2: CES-D Scale > 16	1: Difference in FEV1(%) between patients with depression (50.1%) and without (52.3%) (p-value 0.56) 2: 1: Difference in FEV1(%) between patients with depression (50.4%) and without (52.4%) (p-value 0.59)	No
Omachi TA 2009 [48]	Observational	1202	From an ongoing cohort study, USA, 40–65 years of age	27%	GDS > 6	Multivariate analysis, OR between every 23% decrement in FEV1 (%) and risk of depression (p-value 0.03)	Yes
Howard C 2009 [32]	Observational	59	From a cardiothoracic centre, UK	19%	HADS-D > 11	Correlation coefficient between depression and FEV1(%) -0.120 (p-value > 0.05)	No
Funk GC 2009 [33]	Observational	122	From an outpatient clinic and a hospital ward, Austria, > 18 years	52%	HADS-D > 8	Difference in FEV1(%) between patients with depression (37.0%) and without (52.5%) (p-value 0.001)	Yes
de Voogd JN 2009 [49]	Observational	121	From pulmonary rehabilitation, the Netherlands	16.5%	BDI > 19 Highly depressed	Correlation coefficient between FEV1 (%) and depression r = −0.01 (p-value > 0.05)	No
Halabi S 2011 [50]	Observational	104	From an outpatient clinic, England, Men, > 55 years	34.6%	GDS > 11	Difference in FEV1(%) between patients with depression (42%) and without (44%) (p-value 0.421)	No

Table 2 (continued)

Study	Study type	Subjects	Patient population	Prevalence of depression	Depression definition	Results	Significant?
Horita N 2013 [51]	Observational	84	From three hospitals, Japan, Saturation > 90%. Able to perform 6MWT	38.1%	GDS > 6	Difference in FEV1(%) between patients with depression (38%) and without (51%) (p-value > 0.001)	Yes
Iguchi A 2013 [52]	Observational	74	From pulmonary rehabilitations and in-patients from a pulmonary department, Japan	48.6%	CES-D > 16	Correlation coefficient between FEV1(%) and depression r = -0.29 (p-value 0.01)	Yes
Tselebis A 2013 [36]	Intervention study	101	Patients from a rehabilitation program, Greece, < 80 years old	47.5%	BDI	Correlation coefficient between depression and FEV1(%) 0.01 (p-value > 0.05)	No
Kim KU 2014 [53]	Observational	245	From pulmonary outpatient clinic, Korea	17.6%	CES-D > 24	Difference in FEV1(%) between patients with depression (60.6%) and without (60.4%) (p-value 0.959)	No
Elassal G 2014 [37]	Case–control	80	Out- and inpatients, Egypt	42.5%	HAM-D	Correlation coefficient between FEV1 (%) and depression r = -0.262 (p-value 0.019)	Yes
Miravitlles M 2014 [54]	Observational	836	From outpatient clinics, Spain, > 40 years, > 10 pack years	51.1% moderate to severe	BDI > 10	Difference in FEV1(%) between patients with depression 51.6%) and without (53.6%) (p-value 0.15) Difference in FEV1(%) between patients with mild depression (53.6%) and severe depression (48.9%) (p-value 0.01)	No
Battaglia S 2015 [55]	Observational	326	From an outpatient clinic, Italy	5.8%	Medical history	Prevalence of depression in GOLD 1 (4.3%), GOLD 2 (3.5%), GOLD 3 (5.7%) and GOLD 4 (8%) (p-value > 0.05)	No
Martinez Rivera C 2016 [15]	Observational	115	From outpatient clinics, Spain, > 40 years and > 10 pack years	24.3%	HADS-D > 8	Difference in FEV1(%) between patients with depression (38.8%) and without (46.2%) (p-value 0.02)	Yes

Table 2 (continued)

Study	Study type	Subjects	Patient population	Prevalence of depression	Depression definition	Results	Significant?
Orlandi Le 2016 [56]	Observational	54	From an outpatient clinic, > 40 years, Brazil	22.2%	Mini international neuropsychiatric interview plus	Difference in FEV1(%) between patients with depression (51.9%) and without (43.6%) (p-value 0.108)	No
Tse HN 2016 [57]	Observational	89	From a geriatric and COPD clinic, Hong-Kong, > 60 years	20.22%	GDS > 8	Difference in FEV1(%) between patients with depression (38.7%) and without (46.1%) (p-value 0.15)	No
Allam AH 2017 [39]	Observational	150	From an outpatient clinic, Egypt, > 18 years	14%	HADS-D > 11	Correlation coefficient between FEV1 (%) and depression r = -0.57 (p-value 0.001)	Yes
Biswas D 2017 [16]	Observational	75	From an outpatient clinic, India	54.7%	HAM-D > 8	Difference in FEV1(%) between patients with depression (47%) and without (54.5%) (p-value 0.178)	No
Lee JH 2018 [58]	Observational	211	From a registry, Korea, FEV1 > 50%, > 40 years,	14.2%	PHQ-9 > 27	Difference in FEV1(%) between patients with depression (77.7%) and without (80.1%) (p-value 0.35)	No
Sharma K 2019 [59]	Observational	120	From an outpatient clinic, India, 40–80 years	75%	HAM-D > 8	Difference in FEV1(%) between patients with depression (62.1%) and without (82.5%) (p-value > 0.001)	Yes
Yang K 2020 [60]	Observational	1800	From an American registry	23.5%	PHQ-9 > 4	Odds ratio of depression compared to FEV1 (%) OR = 1.15 (p-value 0,004)	Yes
Choi JS 2021 [61]	Observational	877	From a Korean registry, > 40 years	17.8%	PHQ-9 > 5	Distribution of subjects in GOLD 1–4 in patients with depression (GOLD1 48.1% –GOLD 4 8.9%) and without (GOLD1 51.7% – GOLD 4 3.8%) (p-value 0.019)	Yes

Table 2 (continued)

Study	Study type	Subjects	Patient population	Prevalence of depression	Depression definition	Results	Significant?
Strollo HC 2021 [62]	Observational	1: 220 2: 745	1: From an American cohort, > 40 years, > 10 pack years 2: From an American cohort, 2008–2011, 45–80 years, > 10 pack years,	1: 21.4% 2: 13.0%	1,2: BDI > 9	1: Distribution of subjects in GOLD 1–4 in patient with depression (GOLD1 17.0% –GOLD 4 4.3%) and without (GOLD1 34.1% – GOLD 4 0.1%) (p-value 0.01) 2: Distribution of patients in GOLD 1–4 with depression (GOLD1 11.3% –GOLD 4 19.6%) and without (GOLD1 24.4% –GOLD 4 9.6%) (p-value 0.002)	1: Yes 2: Yes
Hernández-Pérez A 2022 [42]	Observational	291	From an outpatient clinic, Mexico, 60–85 years,	30.9%	HADS-D > 6	Correlation coefficient between FEV1(%) and depression r = -0.03 (p-value 0.592)	No
Yoshida M 2022 [41]	Intervention study	60	From an outpatient clinic, Japan	9.31%	SDS	Distribution of subjects in GOLD 1–4 in patients with depression (GOLD1 8.65% –GOLD 4 7.59%) compared to whole cohort (p-value 0.147)	No
Hong YJ 2023 [43]	Observational	2147	From a cohort study, > 40 years, Korea	27.4%	BDI > 10	Distribution of patients in GOLD 1–4 with depression (GOLD1 8.1% –GOLD 4 12.3%) and without (GOLD1 13.0% –GOLD 4 7.4%) (p-value 0.008)	Yes
Zhang T 2023 [63]	Observational	55	From a hospital ward, China	45.9%	SDS > 50	Difference in FEV1(%) between patients with depression (50.2%) and without (61.8%) (p-value > 0.01)	Yes
Horner A 2023 [64]	Observational	630	From multiple outpatient clinics, Austria > 40 years,	46.2%	PHQ-9 > 5	Regression coefficient between FEV1(%) and depression – 0.06 (p-value < 0.001)	Yes

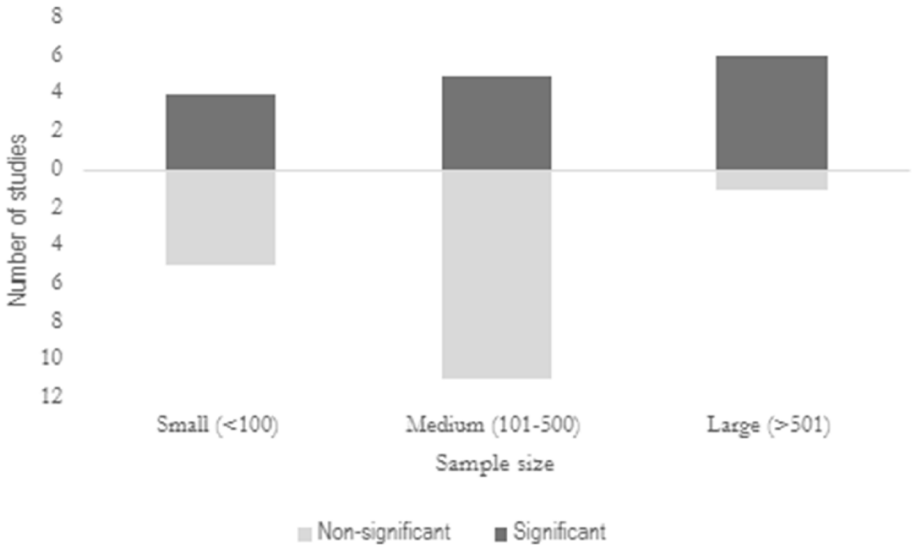

Fig. 4 Number of studies showing significant and non-significant results compared to sample sizes in the depression group. The light downward parts are studies with non-significant results and the dark upward parts are studies showing significant results

patients with stable COPD. Exclusion criteria (other unstable diseases) were not substantially different compared to the remaining studies, as most studies excluded unstable patients in general. Livermore et al. [34] specifically investigated panic disorder, which differs from the other studies. The patients in the study by Allam et al. [39] had an average FEV1(%) of 76.6%, as such mild COPD [17]. This was a considerably higher average FEV1(%) compared to the studies by Livermore et al. [34] with an average FEV1(%) of 52.9% and in one of the largest studies by Hernández-Pérez et al., with an average of 58.0% [42]. It is possible that the rating scales have a different sensitivity and specificity in patients with severe COPD compared to mild COPD, as anxiety often mimics somatic symptoms [66].

The two studies with the youngest average age of study populations found a significant association between anxiety and FEV1(%). The average age of the patients included in the study by Allam et al. [39] was 50.3 years, comparable to the study by Hieba et al. [40] with an average age of 57.2 years, while the average age of the patients in the remaining studies was 60–75 years (Table 2). Previous studies have shown that younger people are better at describing their symptoms as anxiety, which might have an impact on the result of a study [67]. It is outside of the scope of this study to determine if the risk factors of anxiety might be different in a younger population than in an older population, and further studies would be needed to investigate this.

The percentage of females was 25%, 44% and 56% respectively in the studies with significant findings [33, 34, 39]. As the study populations in the studies with non-significant results consisted of 3% to 61% women this does not separate the studies with significant results from the non-significant (Table 2). In this review, there was no indications of specific gender differences in the association between FEV1(%) and anxiety.

Four studies used a direct comparison of average FEV1(%) between patients with and without anxiety. Three studies directly compared the prevalence of anxiety in GOLD group 1–4. Eight studies used different correlation coefficients. The studies showing significant results used both direct comparisons and correlation coefficients [33, 34, 39] and the same applies to the studies showing non-significant positive associations [32, 35, 36, 38, 42]. While this does not support significance implications of the statistical method, as long as it is appropriate, there are other studies that could indicate that choice of statistical method has influenced outcome: Hieba et al. 2021 [40] found a significant association between GOLD group 1–4, i.e. FEV1(%) as a categorical value, but no significant association with FEV1(%) as a continuous value. Opposed to that, a significant association between FEV1(%) and anxiety severity was found, but no association with GOLD groups 1–4 [40]. It is not unreasonable to think that the choice of continuous versus categorical values could influence the results.

A difference between a pooled correlation coefficient and a pooled standardized mean difference was found, as only the latter was significant. Only 11 out of 15 studies could be included in a pooled analysis. The inconsistent results are consistent with the rest of the findings of the study, showing no clear association between FEV1(%) and anxiety. Thus, the clinician should not strictly assess

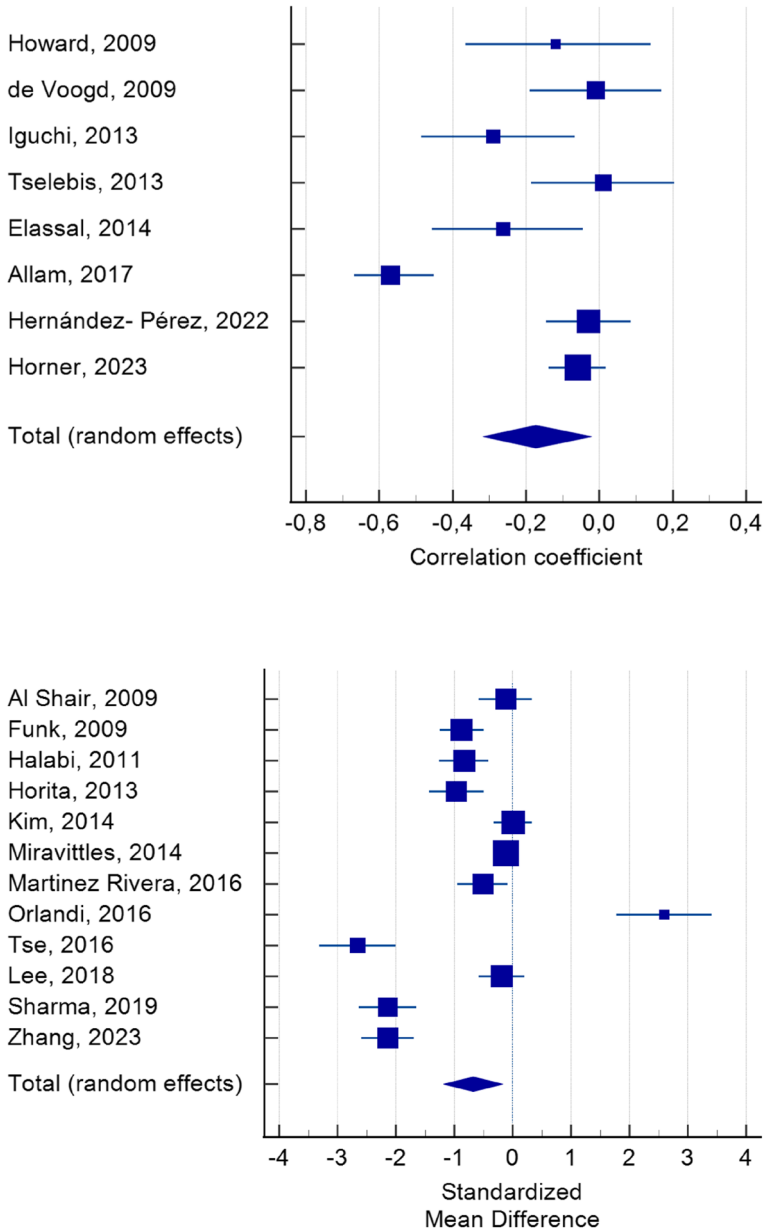

Fig. 5 **A** Pooled correlation coefficients including the studies reporting a correlation coefficient as a measure of association between depression and FEV1(%), **B** Pooled standardized mean difference including the studies reporting mean FEV1(%) in patients with anxiety compared to without depression

the risk of anxiety in patients with COPD on the basis of disease severity. There are several other known risk factors of anxiety in patients with COPD (Sex, symptom burden, socioeconomic status etc.) [7–9, 13, 14], which are possible confounders or effect modulators and might explain the inconsistent findings between studies.

With three studies indicating a negative association and five indicating a positive association this review does not indicate any clear association between anxiety and COPD. The pooled correlation coefficient was non-significant, while the pooled standardized mean difference was significant. Based on these results it is not possible to confidently rule in or out any association between FEV1(%) and anxiety. A meta-analysis in the future could contribute with a higher quality of evidence.

Associations between depression and impairment of pulmonary function.

The definition of depression varies greatly between studies. Nine different scales were used, with BDI, PHQ-9 and HADS-D being the most frequent. Even among studies using the same scale, cut-off values vary greatly. For the studies using GDS, cut off values of for example 6, 8 and 11 have been used [50, 51, 57]. GDS is meaningful in screening for depression in patients > 65 years, as common somatic symptoms in elderly (Loss of appetite, sleep disturbances, tiredness) and possible symptoms of dementia are not included [68]. Some studies using GDS, only including patients over a certain age [48, 55], but two had no age limit or even excluded older patients > 65 years [48, 51]. The use in younger populations is not validated. The sensitivity and specificity of GDS were comparable to the other scales (~ 80%) [68].

The scale yielding the highest proportion of significant studies is PHQ-9, as three out of four studies using this scale, showed significant results [60, 61, 64]. This might be due to the large sample sizes in those studies (630–1800). Studies have shown a specificity and sensitivity using PHQ-9, similar to the other scales [68]. Only one of the four studies using CES-D showed any significant results [45, 47, 52, 53]. CES-D was invented for epidemiologic studies. A review by Smarr Kl et al. showed that the use of CES-C yields a high degree of false positives at cut-off > 16, which three of the studies in this review used, while one used > 24 [45, 47, 52, 53, 68]. On the other hand, CES-D is sensitive to anxiety and might misclassify somatic symptoms as symptoms of psychiatric disease, which have not been shown to be associated to FEV1(%) in this study [68]. Nonetheless, all four studies using CES-D had a small-medium sample size, and may therefore lack statistical power [45, 47, 52, 53]. The heterogeneity in the definition of depression between the studies may be reflected in the prevalence of depression, ranging between 5.8%-75% (Table 2).

Common symptoms of depression include somatic symptoms such as sleep disturbances, appetite loss and weight loss [69]. Studies have shown that sleep disturbances and sedentary behaviour lead to depression in the elderly [70]. It has also previously been shown that 70% of patients with COPD have some degree of sleep disturbances [71]. Patients with COPD have a high degree of sedentary behaviour, which is even higher in case of comorbid depression [54, 72]. Thus, symptoms of depression and burden of illness can be hard to distinguish in patients with COPD, possibly leading to bias or residual confounding. Most studies exclude patients with other severe comorbidities or cognitive impairment, and some exclude the oldest patients [36, 42, 48, 59, 62]. Age, comorbidities, and cognitive impairment that is highly prevalent in COPD [72], also hold a risk of bias, misclassification, and residual confounding. The scores used in the studies to define depression could possibly act as confounders in themselves, but it cannot be confirmed in this review.

The only large study without unambiguous significant results was Miravitlles et al. [54]. Depression was here defined as BDI > 10, which was the most used cut-off value in the studies using BDI. Nevertheless, a prevalence of mild degree of depression of 74.6% and moderate to severe degree of depression of 51.1%, suggests a higher prevalence in this study than most studies in this review (Table 2). In Miravitlles et al., the degree of depression as a continuous value, rather than categorical, was significantly correlated to FEV1(%) [54]. This suggests a significant association between depression and FEV1(%), after all. As most patients were allocated to the depression group, the heterogeneity of this group could be too large to obtain significant results when using categorical values for depression [54].

Almost all the large studies showed a significant association between FEV1(%) and depression, and even the remaining large study showed some significant results [54]. This indicates that a larger sample size is needed to obtain the power to carry studies in affective diseases in patients with COPD. The pooled correlation coefficient and pooled standardized mean difference both showed a significant negative association between FEV1(%) and depression, consistent with the other findings. A future meta-analysis could substantiate the findings, increasing the quality of the evidence.As an association between anxiety and FEV1(%) is not evident, it is important to remember in a clinical setting that even in patients with higher pulmonary function, the clinician should be very aware of the risk of anxiety. Regarding depression, it is important to be aware of the risk increasing with decreasing pulmonary function. Still, the clinician should not forget that there are several risk factors for depression, and it is still very likely to occur in patients with higher pulmonary function [3]. Most studies included in this systematic review only include one measurement of pulmonary function and one assessment of pulmonary function. It would be interesting in a future study to examine whether risk of anxiety or depression increase with decreasing pulmonary function in the same patients in a longitudinal study. This could make it possible to comment on the causation. To the authors' knowledge no studies have investigated how anxiety and depression affects the disability-adjusted life-year and how treatment affects the quality-adjusted life-years [ref]. This would be important knowledge regarding the significance of diagnosing and treating anxiety and depression in COPD, thus a suggestion for future research.

Limitations

As is the case with systematic reviews this review is susceptible to publication bias or outcome reporting bias [74]. Conference abstracts were not included, and it is possible that some data could have been retrieved from those.

Strict selection criteria increase the homogeneity and make it possible to compare studies, but also increase the risk of exclusion-bias. The risk of publication bias is very likely. Three studies mentioned FEV1(%) in a group of COPD patients with and without depression or anxiety but did not perform significance testing and were therefore excluded. FEV1(L) is not useful in this systematic review because it fluctuates with sex, age, ethnicity, and height [17], and sixteen studies were excluded for only reporting FEV1(L). It could lead to bias if FEV1(%) was deliberately excluded from those studies because of non-significance.

There was a great heterogeneity between studies, both in the anxiety and the depression studies. This can be a limitation, as it makes it difficult to compare studies. It is unlikely that ethnicity, culture, age and setting would not affect the prevalence of anxiety and depression [75]. On the other hand, if similar results are found across countries, clinical settings and ages, it could also establish the results, as is the case in the depression group. Many of the included studies had small to modest sample sizes, increasing the risk of lack of power, which lead to an underestimation of the association between anxiety or depression and FEV1(%). The studies in this review are not evenly distributed on nationalities and therefore the potential cultural impact from different nationalities cannot be evaluated in this study.

Two databases were searched when conducting this systematic review. It is possible that other databases could have contributed with additional studies, increasing the quality of the evidence.

A meta-analysis was not conducted. This would have contributed with a greater quality of evidence and negated the meaning of heterogeneity of studies, compared to pooled analysis. A future conduction of a meta-analysis of this topic would yield a higher level of evidence than in the individual studies.

Regarding the Quality Assessment, the studies with smaller sample sizes would be susceptible to bias, which is also reflected in a lower NOS-score. At study level the greatest risks of bias would be the lack of control for confounders, especially symptoms, and unexplained non-respondents. Most studies (23/32) failed to inform about non-respondents, and even if they did, the risk of bias would not be eliminated. A previous study has found a greater risk of depressive symptoms in non-respondents [76] which could also be the case for these studies. Most studies did not control for confounders. The most important confounder would probably be symptoms of COPD, since previous studies have found a link between the symptom burden and both FEV1(%) and anxiety or depression [7–9, 15, 16]. As the risk of bias assessment only was done by one person, the NOS scores could not be validated by comparing the results from more persons, thus increasing the risk of bias. Most studies included patients from outpatient clinics or rehabilitation. Whether this gives a satisfactory external validity depends on the access to these facilities (e.g. waiting lists, referral criteria and payment), which would differ greatly from country to country. Most studies did not describe the settings. It is reasonable to believe that the prevalence of anxiety or depression could depend on whether patients in the study are stable or not, as a greater burden of symptoms earlier has shown to lead to anxiety and depression [7–9, 15, 16]. An influence on the results from selection bias at study level is definitely possible. In general, the quality of the studies was moderate to high, as a certain diagnosis of COPD and appropriate outcome measures were part of inclusion criteria, which makes it reasonable to assume that the impact of bad quality studies on the final results is limited.

Conclusion

Only three out of fifteen studies investigating a correlation between anxiety and FEV1(%) showed significant results, while some even showed a reverse trend, which does not support an association between anxiety and impairment of pulmonary function. However, there may be indications of an association between anxiety and severe COPD.

The review indicates an association between depression and impairment of pulmonary function. However, investigation of any correlation should be investigated in large cohorts.

Abbreviations

COPD	Chronic obstructive pulmonary disease
FEV1(%)	Forced expiratory volume in one second in percentage of expected value
FEV1(L)	Forced expiratory volume in one second in Liters
MRC	Medical Research Council Dyspnoea Scale
6MWT	6-Minute walk test
GOLD	Global Initiative for Chronic Obstructive Lung Disease
STAI	The State Trait Anxiety Inventory
HADS-A	Hospital Anxiety and Depression Scale Anxiety Inventory
ADIS IV	Anxiety Disorder Interview Schedule IV
HAM-A	Hamilton Anxiety Rating Scale
BAI	Beck Anxiety Inventory
GAD	Generalized Anxiety Disorder 7 item
AIR	Anxiety Inventory for Respiratory Disease
CES-D	Center for Epidemiologic Studies Depression Scale
BDI	Becks Depression Inventory
BASDEC	Brief Assessment Schedule Depression Cards
GDS	Geriatric Depression Scale
HADS-D	Hospital anxiety and depression scale for depression

HAM-D	Hamilton Depression Rating Scale (HAM-D)
SDS	Self-rating Depression Scale
PHQ-9	Personal Health Questionnaire 9

Supplementary Information

The online version contains supplementary material available athttps://doi.org/10.1186/s13643-024-02720-z.

Supplementary material 1.

Acknowledgements
Anja Gamskjær Hansen, Medical librarian at the Library of Aalborg University Hospital, Denmark, assisted in creating the search string.

Differences between protocol and review
Since submission of the protocol, the title of the project has been changed from 'correlation between impairment of lung function and risk of depression and anxiety in patients with chronic obstructive pulmonary disease—A systematic review' to 'Association between impairment of lung function and risk of depression and anxiety in patients with chronic obstructive pulmonary disease—A systematic review', as the team agreed that association was more fitting than correlation to describe the review.
As the use of Z-scores when describing pulmonary functions becomes more widespread in clinical settings, it was decided to include studies using Z-scores. Though, no studies using Z-scores were found. It was decided to apply an official risk of bias tool, Newcastle Ottawa Risk Assessment Tool, to obtain an overview over, where the greatest challenges regarding bias were.

Authors' contributions
Johanne Hermann Karlsen (JHK), Kirstine Hermann Jørgensen (KHJ) and Ulla Møller Weinreich (UMW) all contributed to the planning of the study. JHK wrote and submitted the final protocol to PROSPERO. JHK conducted the search with help of a medical librarian and removed duplicates. JHK and KHJ conducted the screening of studies on title and abstract. JHK conducted the full text screening. UMW resolved discrepancies in the selection process as third part. Primary draft for manuscript were prepared by JHK. KHJ and UMW contributed to the content and embodiment of the manuscript.

Funding
Funding was received from the Danish Lung Association. The Danish Lung Association only offered funding and did not take part in the conduction of this review or writing of manuscript.
Danmarks Lungeforening,DLF2022-7,Johanne Hermann Karlsen

Data availability
Entire search string for each publicly available database is available in appendix 1.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 7 March 2024 Accepted: 25 November 2024
Published online: 04 December 2024

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